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## **Current State of the Science: Health Effects and Indoor Environmental Quality**

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## Current State of the Science: Health Effects and Indoor Environmental Quality

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List of abbreviations with definitions:

AER	Air exchange rate
ACH	Air changes per hour
HONO	Nitrous acid
HNO <sub>3</sub>	Nitric acid
hr	Hour
HVAC	Heating, ventilation, and air conditioning
IEQ	Indoor environmental quality

NAAQS	National Ambient Air Quality Standards
NO	Nitric oxide
NO <sub>2</sub>	Nitrogen dioxide
O <sub>3</sub>	Ozone
OH	Hydroxyl
PCR	Polymerase Chain Reaction
PM	Particulate matter
PM <sub>2.5</sub>	Particulate matter 2.5 micrometers or less
Ppm	Parts per million
ppb	Parts per billion
PVC	Poly-vinyl chloride
PCR	Polymerase chain reaction
qPCR	quantitate PCR
SVOC	Semi-volatile organic compound
TVOC	Total volatile organic compound
VOC	Volatile organic compound

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## **Abstract**

Our understanding of the relationship between human health and the indoor environment continues to evolve. Previous research on health and indoor environments has tended to concentrate on discrete pollutant sources and exposures, and on specific disease processes. Recently, there have been efforts to characterize more fully the complex interactions between the health of occupants and the interior spaces they inhabit. In this paper we review recent advances in source characterization, exposure assessment, health effects associated with indoor exposures, and intervention research related to indoor environments. Advances in source characterization include a better understanding of how chemicals are transported and processed within spaces, and the role that other factors such as lighting and building design may play in determining health. Efforts are underway to improve our ability to measure exposures, but this remains a challenge, particularly for biological agents. Studies are also examining the effects of multiple exposures, as well as the effects of exposures on vulnerable populations such as children and the elderly. There are also a number of studies looking at the effects of modifying building design, materials, and operations on occupant health. Identification of research priorities should include input from building designers, operators, and the public health community.

## **Introduction**

Our understanding of health effects related to the indoor environment has evolved over the past decade. In the past, discussions of indoor environmental quality (IEQ) focused on indoor air constituents (primarily particles, bioaerosols, and chemicals), and comfort factors (temperature, air flow, and humidity) (Samet et al. 1998). More recently, we have begun to look at the relationship between the built environment and humans as a complex interplay between building occupants (who they are and what they do) and an array of physical, chemical, biological, and design factors. This evolution in understanding has profound implications for the design and operation of buildings, the uses to which they are put, and the prevention and management of health problems that occur in building occupants.

## **Source Characterization**

Outdoor air pollution is a dynamic system in which the physical and chemical processes affecting the accumulation of pollutants in the atmosphere are constantly changing, largely driven by complex meteorology and photochemistry. In contrast, the usual approach of modeling indoor air pollution considers only pollution source strength and dilution by air exchange, thus treating the indoor environment as a static box in which physical and chemical transformations of indoor air pollutants are absent or negligible. This misconception produces conservative estimates for primary indoor air pollutant concentrations, and ignores the secondary pollutants. In-depth studies of indoor air have shown that the concentration of agents in indoor air is a function of outdoor concentration, indoor source strength, removal and deposition rate within the structure,

indoor mixing and chemical reaction. In the following sections, we use real-world examples to illustrate the dynamic nature of these processes and to discuss the implication of this dynamic environment in assessing exposures and health effects associated with indoor air pollution.

### ***Indoor Production***

Generation of pollutants within the indoor environment may come from primary and secondary sources. Primary sources include: fuel combustion for cooking, heating, and lighting; tobacco smoking; bioeffluents from humans and animals; floor and wall coverings; synthetic paints, glues, polishes and waxes; pesticides; and building products. Another source is the release of gases from solvents used indoors or from water that is used daily for showers, bathing, cooking, and from drinking fountains. Such sources are important for by-products (e.g., chloroform) of chlorination-based water disinfection and radon (McKone and Knezovich 1991; Xu and Weisel 2005). Due to the use of many types of synthetic materials in our daily lives, concentrations of many volatile organic compounds (VOCs) are consistently higher indoors than outdoors in residences and offices in developed countries. For some VOCs such as limonene, indoor levels up to ten times higher than those outdoors are common, even in locations with significant outdoor air pollution sources, such as petrochemical plants (Ott and Roberts 1998; Weisel et al. 2005). Secondary sources refer to indoor chemistry that transforms a set of indoor pollutants, emitted from primary sources or transported from outdoors, to a new set of indoor pollutants, as discussed below.

### ***Outdoor-to-Indoor Transport***

Pollutants of outdoor origin, including those present in the outdoor air and those released from soil sources, can be transported indoors via building openings and cracks (Garbesi et al. 1999; Nazaroff 2004). Attempts have been made to estimate the fraction of measured indoor concentration contributed by outdoor air, due to the outdoor-to-indoor transport process (Ott et al. 2000; Thatcher and Layton 1995). One such study, the Exposures of Adult Urban Populations in Europe Study (EXPOLIS), compared concentrations of ambient particulate matter less than or equal to 2.5 micrometers (PM<sub>2.5</sub>), its 16 elemental constituents and black carbon, 30 VOCs, and CO among urban adult populations in 7 European cities. The study examined exposures in workplaces, residential outdoor and indoor air, and separated workday and leisure time (Jantunen et al. 1998). EXPOLIS data from Helsinki, Finland showed the infiltration factor (the proportion of outdoor PM found indoors) for PM<sub>2.5</sub> averaged 0.64 for residential structures, 0.47 for workplaces, and 0.35 for a subsample of office buildings constructed after 1990 (Hänninen et al. 2004b, 2005). In another study, the Relationship of Outdoor, Indoor, and Person Air (RIOPA), fractions of measured indoor concentration contributed by outdoor air for PM<sub>2.5</sub> and each of 24 VOCs including 10 aldehydes and ketones were estimated for 310 residences located in three US cities (Weisel et al. 2005). The median fractions of measured indoor concentration contributed by outdoor air for compounds with dominant indoor sources were less than 50%, e.g., 13% for *d*-limonene (a common cleaning solvent), 20% for chloroform (a byproduct of drinking water disinfection), 31% for  $\alpha$ -pinene and 20% for  $\beta$ -pinene (ingredients of synthetic paints), and 19% for formaldehyde (released from building/furnishing materials). For the compounds with

sole or dominant outdoor sources (e.g., methyl *tert* butyl ether, carbon tetrachloride, and trichloroethylene), the fractions were about 100%, as expected. The fractions for PM<sub>2.5</sub> had a median of 56%, 25<sup>th</sup> percentile of 46%, and 75<sup>th</sup> percentile of 93% across the RIOPA homes (Meng et al. 2005; Weisel et al. 2005).

Significant inter-home variability in fractions of measured indoor concentrations contributed by outdoor air has been observed for PM<sub>2.5</sub> and most of the VOCs in the RIOPA study. This finding has important implications for air pollution epidemiologic studies using concentrations measured at outdoor locations. Numerous exposure studies have shown poor correlations between personal exposure or residential indoor concentration and outdoor concentrations, indicating the observed associations between adverse health effects and PM concentrations measured at fixed outdoor sites do not necessarily represent the exposure-response relationships (Adgate et al. 2004; Clayton et al. 1993). While attempts have been made to differentiate PM of outdoor origin from PM of indoor origin, analyses have been complicated because the fraction of indoor species contributed by outdoor air depends not only on outdoor concentration, but also on home-specific parameters including air exchange rate, indoor generation rate, removal rate, and house volume (Meng et al. 2005; Thomas et al. 1993; Wallace et al. 1991).

Outdoor-to-indoor transport of very reactive chemical species has often been considered unimportant. An example is ground-level ozone that is formed via photochemical reactions and has elevated concentration in polluted atmospheres during photochemical smog episodes. Ozone, like PM, is regulated in the US as a criteria pollutant. Due to its high reactivity, only a fraction of ozone can penetrate a building envelope. This fraction had been considered insignificant to cause any exposure concerns

until 1989 when Weschler showed that indoor exposure to ozone can easily surpass outdoor exposure (Weschler et al. 1989). Under moderate air exchange rates ( $\sim 0.5 \text{ hr}^{-1}$ ), indoor ozone concentrations may be 20% - 30% of corresponding outdoor concentrations. Under high air exchange rates ( $> 1 \text{ hr}^{-1}$ ), indoor ozone levels can be 50% - 70% of outdoor levels. In a study carried out in 6 homes located in suburban New Jersey, indoor ozone concentrations were 22% -66% of outdoor levels during afternoon hours (Zhang et al. 1994). In summer time, 50% of the schools measured in Mexico City had indoor ozone levels  $> 113 \text{ ppb}$  (Gold et al. 1996). It is reasonably conservative to state that indoor ozone levels  $> 20 \text{ ppb}$  are common when outdoor ozone concentrations are elevated. Ozone concentration at 20 ppb may not be high enough to cause health concerns due to direct ozone exposure, but this ozone level can be sufficient to drive a complex set of indoor chemical reactions. When ozone generators (so-called “air purifiers”) are used at designed ozone generation rates of tens to thousands of milligram per hour, indoor ozone concentrations can be in the ppm levels in a room with typical volume and air exchange rate.

Particle sources include both indoor, home, and residential sources, although recent research has shown that indoor (workplace and residential) contributions to total exposures may be underestimated compared with outdoor sources such as traffic (BeruBe et al. 2004; Koistinen et al. 2004). This appears to depend on the character of the particle; combustion-derived particles may be due more to outdoor sources, while other particles (for example, soil-derived particles) may be related to resuspension of particles during a host of indoor activities (Ferro et al. 2004; Larson et al. 2004). Recent experiments have shown that a wide range of indoor activities can result in considerable

generation of particulate matter (Afshari et al. 2005). Models of indoor particulate matter exposure have been developed to account for both indoor and outdoor sources, as well as mixing, transport, and removal (Georgopoulos et al. 2005; Nazaroff 2004).

### ***Indoor-to-Outdoor Transport***

Ventilation is the primary factor affecting indoor-to-outdoor transport of indoor generated pollutants. Ventilation is necessary to reduce concentrations of pollutants generated indoors, but it is also necessary to reduce the time available for chemical reactions among indoor pollutants. One of the reasons offered to support the conventional view of indoor chemistry being insignificant is that chemical reactions among indoor pollutants are too slow to complete with air exchange processes. While this may be true when the air exchange rate (AER, typically expressed as air changes per hour) is high, a variety of chemical reactions can take place at AERs typical of today's residences and offices. Since the late 1970s, the airtight design of buildings, driven mainly by energy conservation, has resulted in reduced AERs. Based on approximately 4590 measurements of residential AERs conducted across the US, Pandian et al reported that the mean, median and standard deviations of AERs were 0.55, 0.42 and  $0.47\text{ h}^{-1}$ , respectively, for the northeastern region, and 0.71, 0.62 and 0.56 for the southeastern region of the US (Pandian et al. 1998). AERs of this magnitude are undesirable for removing air pollutants that originate indoors and are low enough for certain chemical reactions to occur.

## ***Indoor Chemistry***

Pollutants can be removed from indoor air through both physical and chemical processes. Physical processes that can result in pollutant removal (in addition to transport outdoors) include phase change, adsorption or absorption, or dissolving in water or organic films. Recently there has been considerable research interest in removal of pollutants through chemical reactions.

“Indoor chemistry” has been defined as reactions involving indoor pollutants, occurring either in the gas phase or on surfaces (Weschler et al. 2005). For a chemical reaction to influence the indoor environment, the rate of the reaction must be fast enough to compete with AER. These chemical reaction processes represent sinks for the reactants (primary indoor pollutants) and sources of new reaction products (secondary indoor pollutants). The products may predominate in the air or on the surface. Removal does not necessarily happen in a simple linear fashion; for example, semi-volatile organic compounds can undergo an initial removal followed by a secondary increase due to resuspension of the compounds adsorbed on particles (Lioy 2006).

Both gas-phase reactions and surface reactions have been identified that can occur under typical indoor conditions. The most extensively studied gas-phase reactions are oxidation reactions involving ozone and free radicals. Ozone ( $O_3$ ) drives most indoor oxidation chemistry because it can react at meaningful rates with nitric oxide (NO), nitrogen dioxide ( $NO_2$ ), and unsaturated organic compounds (e.g., terpenes, terpenoids, sesquiterpenes, unsaturated fatty acids) to yield reactive intermediates, the hydroxyl radical ( $OH$ ), the nitrate radical ( $NO_3$ ) and oxygenated organic compounds (Weschler and Shields 1996). Reactions of  $O_3$  with  $NO_2$ , in the absence of sunlight, form the  $NO_3$

radical that further reacts with VOCs, leading to the formation of indoor nitric acid. The  $\text{NO}_3$  radical can also react with  $\text{NO}_2$  to form dinitrogen pentaoxide ( $\text{N}_2\text{O}_5$ ) that undergoes hydrolysis, another pathway of nitric acid formation (Weschler et al. 1992). When  $\text{O}_3$  and  $\text{NO}_2$  are present simultaneously, indoor  $\text{NO}_3$  may be the dominant indoor oxidant that effectively reacts with nearly all indoor VOCs. The role of indoor  $\text{NO}_3$  chemistry in transforming indoor air pollutants remains to be evaluated.

Several terpenes, especially d-limonene and  $\alpha$ -pinene, are present at substantially higher concentrations indoors compared with outdoors. These terpenes react readily with ozone under typical or realistic indoor conditions to initiate a series of complex chemical reactions, e.g., at an  $\text{O}_3$  concentration of 20 ppb, the rate constant for  $\text{O}_3$  reaction with d-limonene and  $\alpha$ -pinene is  $\sim 0.36 \text{ hr}^{-1}$  and  $\sim 0.15 \text{ hr}^{-1}$  (Fan et al. 2003). Products of these reactions are found in both the gas and particle phases. Gas phase stable products include aldehydes, carboxylic acids, potentially allergenic peroxides and hydroperoxides (Fan et al. 2003). In one experiment where  $\text{O}_3$  ( $\sim 41 \text{ ppb}$ ) was mixed with a VOC mixture comprising 23 commonly found VOCs, the resulting peak concentration of ultrafine and fine particles was  $\sim 100 \mu\text{g}/\text{m}^3$  (Fan et al. 2005). Although attempts have been made to chemically identify the resulting particles, the majority of the particle mass could not be explained by the compounds identified thus far (Fan et al. 2003). It will be even more challenging to identify the short-lived, highly reactive, thermally labile or highly oxidized species that are formed in this complex reaction system. Unstable products of the ozone-terpene reactions include reactive intermediates and the hydroxyl radical. Hydroxyl radicals resulting from these indoor reactions can reach levels higher than typical

nighttime outdoor concentrations, and thus react with other indoor VOCs with which ozone reacts too slowly to be of any practical significance (Weschler and Shields 1996).

The formation of particles via ozone-driven indoor chemistry has two implications. Firstly, in an analysis of indoor particles measured in residences located in several US cities, 25% of indoor PM<sub>2.5</sub> could not be explained with known sources (Wallace 1996). Indoor chemistry was not considered in the analysis and might explain at least part of the unknown sources. Secondly, because O<sub>3</sub> and fine particles are co-generated outdoors during photochemical episodes, indoor particles resulting from indoor ozone/VOC reactions can vary coincidentally with the variations of outdoor summertime fine particles. This will certainly complicate the effort to separate PM of outdoor origin from PM of indoor origin. It should also be noted that source characterization may vary significantly, depending on the size of the particles (Koistinen et al. 2004).

A second type of indoor chemistry involves surface reactions. Outdoor aerosol surfaces play an important role in atmospheric chemistry. The importance of surface reactions indoors is easily recognized given that surface-to-volume ratios indoors are much larger than outdoors (roughly 3 versus 0.01 m<sup>2</sup>/m<sup>3</sup>). Indeed, indoor surfaces may be ideal for substance sorption and for water condensation. Surface water film can react with indoor NO<sub>2</sub>, a major product of natural gas combustion, to form nitrous acid (HONO) and nitric acid (HNO<sub>3</sub>). The resulting nitrous acid is released into the air as gas-phase HONO while nitric acid remains on surfaces as an HNO<sub>3</sub>-H<sub>2</sub>O complex (Dubowski et al. 2004). The latter yields possible acidic, oxidizing, and nitrating surface films on interior walls. Ozone reacts with unsaturated VOCs contained in surface coatings at a

faster rate than when it reacts with the same compounds in the gas phase (Reiss et al. 1995).

Indoor surfaces, including building materials, wall cavities, ducts, skin, clothing, dust, and airborne particles are very diverse, and are a determining factor of indoor surface chemistry. They affect HONO formation via surface-NO<sub>2</sub> chemistry (Wainman et al. 2001). Complex physical and chemical processes involving surfaces include sorption, redox reactions, acid-base chemistry and hydrolysis (Nazaroff and Singer 2004). For example, diphthalate esters (plasticizers contained in PVC floors) can undergo hydrolysis to form alcohols and monoesters. Aldehydes are emitted, at concentrations exceeding their odor thresholds, when O<sub>3</sub> interacts with carpets (Morrison and Nazaroff 2002).

Building materials contain a large number of reactive constituents that can be released into the indoor air along with secondary products, including terpenoids, aliphatic aldehydes, phthalates, phenol, mono- and dicarboxylic acids, diisocyanates and various photoinitiators. Photoinitiators, contained in UV curable coatings, can undergo decomposition to generate free radicals, and some (for example, benzaldehyde and cyclohexanone) are precursors of odorous products (Salthammer et al. 2002). In a study conducted in German houses constructed with wooden studs treated with pentachlorophenol (PCP), it was found that over time PCP had been transformed to tetrachloroanisole, a compound of highly undesirable odor (Gunschera et al. 2004).

Indoor oxidation chemistry is largely driven by O<sub>3</sub> reactions with unsaturated VOCs and perhaps with NO<sub>2</sub> as well. Given that ozone levels have been rising in many areas, that indoor use of unsaturated VOCs (e.g., terpenes) has been on the rise, and that

AERs have been decreasing, indoor oxidation chemistry has likely increased over the past several decades.

## **Exposure Assessment**

Much remains to be learned about exposure assessment in indoor environments. Part of the challenge is to account for the relative contributions of both indoor and outdoor exposures. This has important implications as indoor and outdoor exposures are often regulated very differently. Studies suggest that while indoor environmental measurements provide a better estimate of personal exposure than outdoor monitoring of VOCs, neither indoor nor outdoor environmental sampling (together or individually) is a good predictor of personal exposures (assessed by personal sampling and blood VOC concentrations) (Sexton et al. 2004, 2005).

Exposure assessment for biological agents is even more challenging than for particulate and chemical exposures. New and more accurate identification methods to identify molds are under development. Currently, polymerase chain reaction (PCR) methods are used in which the target DNA from building material is used as a template. In quantitative PCR (qPCR), quantitative data on the presence of viable and dead molds can be obtained, information not possible with the present culture methods (Cruz and Stetzenbach 2004; Meklin et al. 2004). These new methods are not yet complete and need to be evaluated (Keswani et al. 2005; McDevitt et al. 2004; Vesper et al. 2004). Even if fungal and mold species can be identified more accurately in the environment, there are as yet no reliable markers of human exposure or dose for these and other

biological agents; some efforts are underway to assess exposure using chemical markers or immunologic markers (Schmeichel 2006; Sebastian et al. 2005).

## **Health Effects**

In this section we review recent findings on specific agents and mixtures of pollutants. Some of the most significant advances have been made in our understanding of the mechanism of inflammation, and its role in mediating the responses to a wide variety of environmental stressors.

### ***Particulate Matter***

Particulate air pollution has long been linked to both acute and chronic health effects, including asthma (e.g., mineral and organic dusts), cardiac disease (e.g., tobacco smoke and ambient air PM2.5), and other conditions (Pope et al. 1991; Viegi et al. 2004). Recent attention has focused on the ability of particulate matter to potentiate the effects of common allergens, promoting IgE production (Karol 2002). Fine particles have been shown to decrease FEV1 in asthmatic schoolchildren (Delfino et al. 2004). Although particles have been shown to increase cardiovascular mortality, the specific mechanisms by which this occurs have yet to be clarified. Recent investigations have focused on possible effects on heart rate variability (Magari et al. 2002; Pope et al. 1999). Particulate matter, especially products of combustion, has also been linked to the development of cancer, although the exact relationship is still under active investigation (Vineis and Husgafvel-Pursiainen 2005).

Most studies of particulate matter have focused on ambient (outdoor) exposures and their relationship to hospital admissions and mortality. The contribution and significance of indoor particulate matter, which may differ substantially in composition from outdoor particulates, has yet to be fully explored (Bell et al. 2004; Morris 2001). Few studies have described the attributable risk of adverse health effects from indoor sources of particles, but some are attempting to quantify the relative contributions of indoor and outdoor particulate matter (and other toxins) in greater detail, to aid risk and exposure models (Weisel et al. 2005).

### ***Chemicals***

Chemicals of interest in the built environment include volatile and semi-volatile organic compounds, pesticides, and some chemicals produced during combustion (carbon monoxide, nitrogen oxides). Initially, interest in chemicals in indoor environments focused primarily on irritant and toxic properties of individual chemicals such as volatile organic compounds (VOCs) and combustion products. Concerns were also raised about the potential for chronic health effects (primarily cancer) related to exposures to organic compounds. There is interest also in the health effects from plastics and plasticizers. Chemical constituents of plastics have been found in household dust, and studies suggest these plasticizers may be related to allergic diseases in children (Bornehag et al. 2004b, 2005; Oie et al. 1997). Chemical processing inside structures also contributes to adverse health effects from indoor chemicals (Weschler 2004).

The relationship between irritation, stress, and perceived health effects of VOC exposures has gained increased attention. In one recent study, controlled exposures to

VOCs, with and without ozone, did not significantly affect health effects compared with performance of a stress-inducing task (Fiedler et al. 2005).

The relationship of VOCs to asthma, particularly in children, remains controversial. A population-based case control study of asthmatic and non-asthmatic children (ages 6 months to 3 years) in Australia found that the adjusted odds ratios for asthma increased with increasing concentration of VOCs (particularly benzene, toluene, ethylbenzene, and xylene) (Rumchev et al. 2004). By contrast, a study in the United Kingdom found that VOC exposure (except formaldehyde) was not associated with an increased risk of wheezing illness, while dampness was significantly associated with wheezing illness (Venn et al. 2003). Several factors could account for inconsistencies between observational and interventional studies of home exposures to VOCs and asthma risk, including confounding, small effect levels, or chronicity of exposure (Dales and Raizenne 2004).

Polybrominated diphenyl ethers commonly used in flame retardants in consumer products can concentrate in house dust, and thus are potentially available to be ingested by occupants (Gevao et al. 2006). Similar results have been obtained for a variety of chemicals used in consumer products, indicating the importance of examining not only building components, but also furnishings and contents of the indoor environment as sources of exposure (Marklund et al. 2003).

## ***Biological Agents***

### **Animal Antigens**

Allergy to indoor agents can cause frequent and severe health problems, especially in children. Animal allergens are found commonly indoors, even where animals are not present. For example, assessment of cat, dog and mite allergens in settled dust in schools and day-care centers in Oslo, Norway revealed most samples contained detectable amounts of cat and dog allergens. Allergens were detected in mattress and floor dust (day-care centers), and curtain and floor dust (schools). The levels of cat and dog allergens in school floor dust were associated with the number of pupils with animals at home. By contrast, <1% of the samples had measurable levels of mite allergen Der p 1. Endotoxin levels were also assessed. Levels of endotoxin tended to be higher in dust from floors ( $1.4 \text{ ng/m}^2$ ) compared with that from mattresses ( $0.9 \text{ ng/m}^2$ ). Mattresses in day-care centers are reservoirs of cat and dog allergens and should be cleaned frequently (Instanes et al. 2005).

In most communities, avoiding cats in the home would not decrease the prevalence of sensitization to cats because cat allergen is distributed in schools, other public buildings, and homes without a cat. Evidence that children or adults who make a modified TH2 response (IgG and IgG4 antibody without IgE) are not at increased risk of asthma supports the role of IgE in asthma (Erwin et al. 2005).

## **Biological Hazards Associated with Damp Indoor Environments**

There is a large and growing literature on the health effects of biological agents typically found in damp indoor environments (Bornehag et al. 2001, 2004a). An Institute of Medicine committee concluded that there was sufficient evidence of association of damp indoor spaces with various upper and lower respiratory tract symptoms in adults and children. Molds and other specific biological agents were associated with a number of conditions including hypersensitivity pneumonitis in susceptible persons. The committee noted that in many cases, and for many conditions, there was still insufficient evidence to conclude that such an association exists (Institute of Medicine Committee on Damp Indoor Spaces and Health 2004).

The clinical effects of human exposure to mold spores were studied in sensitive subjects who had previously experienced potentially building-related symptoms at work. A highly controlled dose of fungal material was aerosolized directly from wet building materials. In a double-blinded study, eight sensitive school employees were exposed to *Penicillium chrysogenum* or *Trichoderma harzianum* spores for 6 min on three separate days. A statistically significant rise in symptoms from mucous membranes was assessed. This short-term exposure to high concentrations of two different molds induced no more reactions than exposure to placebo. Long-term experimental exposure studies on larger number of subjects would be needed to rule out an effect of mold exposure (Meyer et al. 2005).

One area in which the IOM panel felt there was insufficient evidence to conclude whether an association or causal relationship concerned molds and a number of systemic conditions that have been alleged to be related to mycotoxins (Fischer and Dott 2003).

Molds can produce toxic metabolites known as mycotoxins. Over 400 mycotoxins have been described, most produced by species occurring on food. Many of the molds found indoors are similar to those on food and therefore are also considered potential mycotoxin producers. It is important to note that mycotoxin production is dependent both on the growth conditions and the substrate and therefore only a limited number of species are known to produce toxic compounds when grown on building or in house materials (Nielsen et al. 2002). The most well-known species is *Stachybotrys chartarum* but there has been considerable controversy regarding the toxic potential of *Stachybotrys chartarum*. It is essential to be careful when dealing with fungal problems caused by *Stachybotrys* or related fungi. Although the species *S. chartarum* is well known, there are about 17 other different species of *Stachybotrys* and the related *Memnoniella* (Jarvis 2003; Jong and David 1976).

Research on the chemistry of *Stachybotrys* toxins is progressing, to identify the chemical properties of species occurring in indoor environments. An excellent review of the toxins of *Stachybotrys chartarum* describes a variety of secondary metabolites including trichothecenes, triprenylated phenols and a new class of diterpenoids called atranones produced by the fungus (Jarvis 2003). Two chemotypes were found in *Stachybotrys*. The very toxic macrocyclic trichothecenes were detected in one third of the isolates, less toxic, simple trichothecenes and a new class of atranones were found in the remaining two third of the isolates. Atranones also possess significant biological activity (J.D. Miller, personal communication). Species of *Chaetomium* and *Aspergillus* *vesicolor* are also potential toxin producers.

The clinical effects of mycotoxins have been alleged to include respiratory, neurologic, immunologic, dermatologic, gastrointestinal, and irritant effects, among others (Kuhn and Ghannoum 2003; Laumbach and Kipen 2005). Despite the absence of validated markers of exposure, there have been efforts to understand the relationship between mold exposures and chronic non-allergic health effects. There have also been trials of empiric therapies for mold-exposed individuals, including a series of patients treated with cholestyramine (Shoemaker and House 2005). There remains a lack of consensus regarding the systemic effects of mold exposures (Terr 2004). One of the limiting factors in this research is reliable, validated markers of exposure to either molds or the putative mycotoxins.

In addition to intact molds and fungi, (1-->3)- $\beta$ -D-glucans are non-allergenic structural cell wall components of most fungi that have been suspected of playing a causal role in the development of respiratory symptoms associated with indoor fungal exposure. Current epidemiological data do not permit conclusions to be drawn regarding the presence (or absence) of such an association between exposure and specific adverse health effects, or which specific immunological mechanisms underlie the presumed health effects (Douwes 2005).

Other biological hazards associated with indoor environments include bacteria, viruses, and other organisms. While the association of *Legionella* with building water systems is well known, humidification systems carry risks for development of a variety of organisms capable of causing acute inflammatory responses, as well as infection (Koschel et al. 2005). In addition, the design and operation of HVAC systems may have

significant impact on the distribution of and subsequent exposures to aerosolized infectious agents (Li et al. 2005a; Li et al. 2005b).

### ***Interactions and Multiple Exposures***

Investigators have begun to measure multiple pollutants present within the same environment, including particles, combustion products, photochemical smog products, and allergens (Breysse et al. 2005; Hänninen et al. 2004a). In part this is because health effects are often related to multiple exposures, and because many experimental interventions affect more than one exposure and agent. There are also important interactions between exposures to pollutants and other hazards such as infectious agents. Exposures to O<sub>3</sub> and NO<sub>2</sub> have been shown to increase airway epithelial cell cytokine production (Spannhake et al. 2002). Studies have also demonstrated interactions between particles and other contaminants such as ozone that can potentiate the health effects of the two concomitant exposures (D'Amato et al. 2005; Harkema and Wagner 2005; Mar et al. 2005; Molhave et al. 2005). These findings suggest there may be additional benefits to interventions that reduce cumulative exposures to several pollutants, compared with interventions focusing on only one exposure.

### ***Building Design and Health***

There is growing interest in examining the interaction of building design and health (Cummins and Jackson 2001). Physical and design characteristics of built structures (lighting, heating, ergonomics, noise, design) may create additional exposures that might contribute to health and comfort. Some of these factors may also play a role in

chronic health effects. For example, there is evidence that suppression of melatonin by nocturnal artificial lighting may play a role in breast and colon cancer development (Pauley 2004; Stevens 2005).

Research in office buildings, which has tended to focus on health and productivity, has begun to move beyond indoor air to issues such as office design and acoustics (De Croon et al. 2005). There is a growing literature on school design and injury prevention, with more recent research on physical activity, obesity, and the implications of school design for the development of chronic diseases in later life (Sallis and Glanz 2006). There is limited literature on student achievement (Sexton et al. 2000). Finally, studies of residential building design have examined a range of health outcomes related to building design, notably injury, but also mental health and other outcomes (Weich et al. 2002; Bonnefoy et al. 2003).

## **Intervention Studies**

A number of investigators have started to examine the effectiveness of environmental modification and education in reducing asthma severity. Examples include the use of air filters (Francis et al. 2003; Kilburn et al. 2003); pest management (McConnell et al. 2003), and education coupled with environmental modification (Krieger et al. 2002; Morgan et al. 2004; Tobias et al. 2004). Most of the interventions focus on control of more than one exposure, and have a relatively short duration.

Another study showed that use of ultra-violet germicidal irradiation within the HVAC system could reduce irritation symptoms in office workers (Menzies et al. 2003). This study was a crossover design in which subjects were blinded as to whether the

intervention was in effect, and it used both symptom reporting and objective measures as outcomes. Although it did not examine all the potential limitations and side effects of the intervention, it provides a useful example of the kinds of studies that may be needed to evaluate intervention strategies.

## **Conclusion**

It is increasingly apparent that indoor environments are unique and contain significant exposures that can affect the health of occupants. The exposures are the result of complex interactions between the structure, building systems, furnishings, the outdoor environment, and the building occupants and their activities. As people spend more time indoors, the opportunities for significant health effects due to these exposures increase. So too does the need for research into the circumstances that make exposures more likely, and the effectiveness of interventions to reduce the exposures. Interventions may involve difficult tradeoffs, such as increased ventilation versus the need for energy efficiency. In addition, more research is needed on the interactions of multiple exposures, and the risks to certain populations (such as children, the elderly, or socioeconomically disadvantaged populations). Identification of research priorities should include input from building designers, operators, and the public health community. Research on interventions should examine a range of outcomes and potential tradeoffs and confounders, and does not necessarily need to await the identification of specific causal agents. Research is also needed on better measures of dose, particularly for biological agents.

## References

Adgate JL, Church TR, Ryan AD, Ramachandran G, Fredrickson AL, Stock TH, et al. 2004. Outdoor, indoor, and personal exposure to VOCs in children. *Environ Health Perspect* 112:1386-1392.

Afshari A, Matson U, Ekberg LE. 2005. Characterization of indoor sources of fine and ultrafine particles: a study conducted in a full-scale chamber. *Indoor Air* 15:141-150.

Bell ML, Samet JM, Dominici F. 2004. Time-series studies of particulate matter. *Annu Rev Public Health* 25:247-80.:247-280.

BeruBe KA, Sexton KJ, Jones TP, Moreno T, Anderson S, Richards RJ. 2004. The spatial and temporal variations in PM10 mass from six UK homes. *Sci Total Environ* 324:41-53.

Bonnefoy XR, Braubach M, Moissonnier B, Monolbaev K, Robbel N. 2003. Housing and health in Europe: preliminary results of a pan-European study. *Am J Public Health* 93:1559-1563.

Bornehag CG, Blomquist G, Gyntelberg F, Jarvholm B, Malmberg P, Nordvall L, et al. 2001. Dampness in buildings and health. Nordic interdisciplinary review of the scientific evidence on associations between exposure to "dampness" in buildings and health effects (NORDDAMP). *Indoor Air* 11:72-86.

Bornehag CG, Lundgren B, Weschler CJ, Sigsgaard T, Hagerhed-Engman L, Sundell J. 2005. Phthalates in indoor dust and their association with building characteristics. Environ Health Perspect 113:1399-1404.

Bornehag CG, Sundell J, Bonini S, Custovic A, Malmberg P, Skerfving S, et al. 2004a. Dampness in buildings as a risk factor for health effects, EUROEXPO: a multidisciplinary review of the literature (1998-2000) on dampness and mite exposure in buildings and health effects. Indoor Air 14:243-257.

Bornehag CG, Sundell J, Weschler CJ, Sigsgaard T, Lundgren B, Hasselgren M, et al. 2004b. The association between asthma and allergic symptoms in children and phthalates in house dust: a nested case-control study. Environ Health Perspect 112:1393-1397.

Breysse PN, Buckley TJ, Williams D, Beck CM, Jo SJ, Merriman B, et al. 2005. Indoor exposures to air pollutants and allergens in the homes of asthmatic children in inner-city Baltimore. Environ Res 98:167-176.

Clayton CA, Perritt RL, Pellizzari ED, Thomas KW, Whitmore RW, Wallace LA, et al. 1993. Particle Total Exposure Assessment Methodology (PTEAM) study: distributions of aerosol and elemental concentrations in personal, indoor, and outdoor air samples in a southern California community. J Expo Anal Environ Epidemiol 3:227-250.

Cruz P, Stetzenbach LD. 2004. Specific detection of fungi associated with SBS when using quantitative polymerase chain reaction. Adv Appl Microbiol 55:437-449.

Cummins SK, Jackson RJ. 2001. The built environment and children's health. *Pediatr Clin North Am* 48:1241-52, x.

D'Amato G, Liccardi G, D'Amato M, Holgate S. 2005. Environmental risk factors and allergic bronchial asthma. *Clin Exp Allergy* 35:1113-1124.

Dales R, Raizenne M. 2004. Residential exposure to volatile organic compounds and asthma. *J Asthma* 41:259-270.

De Croon EM, Sluiter JK, Kuijer PP, Frings-Dresen MH. 2005. The effect of office concepts on worker health and performance: a systematic review of the literature. *Ergonomics* 48:119-134.

Delfino RJ, Quintana PJ, Floro J, Gastanaga VM, Samimi BS, Kleinman MT, et al. 2004. Association of FEV1 in asthmatic children with personal and microenvironmental exposure to airborne particulate matter. *Environ Health Perspect* 112:932-941.

Douwes J. 2005. (1-->3)-beta-D-glucans and respiratory health: a review of the scientific evidence. *Indoor Air* 15:160-169.

Dubowski Y, Sumner AL, Menke EJ. 2004. Interactions of gaseous nitric acid with surfaces of environmental interest. *Physical Chemistry and Chemical Physics* 6:3879-3888.

Erwin EA, Custis N, Ronmark E, Wickens K, Sporik R, Woodfolk JA, Platts-Mills TA. 2005. Asthma and indoor air: contrasts in the dose response to cat and dust-mite. Indoor Air 15 Suppl 10:33-39.

Fan Z, Liou P, Weschler C, Fiedler N, Kipen H, Zhang J. 2003. Ozone-initiated reactions with mixtures of volatile organic compounds under simulated indoor conditions. Environ Sci Technol 37:1811-1821.

Fan Z, Weschler CJ, Han I, Zhang J. 2005. Co-formation of hydroperoxides and ultra-fine particles during the reactions of ozone with a complex VOC mixture under simulated indoor conditions. Atmospheric Environment 39:5171-5182.

Ferro AR, Kopperud RJ, Hildemann LM. 2004. Source strengths for indoor human activities that resuspend particulate matter. Environ Sci Technol 38:1759-1764.

Fiedler N, Laumbach R, Kelly-McNeil K, Liou P, Fan ZH, Zhang J, et al. 2005. Health effects of a mixture of indoor air volatile organics, their ozone oxidation products, and stress. Environ Health Perspect 113:1542-1548.

Fischer G, Dott W. 2003. Relevance of airborne fungi and their secondary metabolites for environmental, occupational and indoor hygiene. Arch Microbiol 179:75-82.

Francis H, Fletcher G, Anthony C, Pickering C, Oldham L, Hadley E, et al. 2003. Clinical effects of air filters in homes of asthmatic adults sensitized and exposed to pet allergens. Clin Exp Allergy 33:101-105.

Garbesi K, Robinson AL, Sextro RG, Nazaroff WW. 1999. Radon entry into houses: the importance of scale-dependent permeability. *Health Phys* 77:183-191.

Georgopoulos PG, Wang SW, Vyas VM, Sun Q, Burke J, Vedantham R, et al. 2005. A source-to-dose assessment of population exposures to fine PM and ozone in Philadelphia, PA, during a summer 1999 episode. *J Expo Anal Environ Epidemiol* 15:439-457.

Gevao B, Al-Bahloul M, Al-Ghadban AN, Al-Omair A, Ali L, Zafar J, et al. 2006. House dust as a source of human exposure to polybrominated diphenyl ethers in Kuwait. *Chemosphere*.

Gold DR, Allen G, Damokosh A, Serrano P, Hayes C, Castillejos M. 1996. Comparison of outdoor and classroom ozone exposures for school children in Mexico City. *J Air Waste Manag Assoc* 46:335-342.

Gunschera J, Fuhrmann F, Salthammer T, Schulze A, Uhde E. 2004. Formation and emission of chloroanisoles as indoor pollutants. *Environ Sci Pollut Res Int* 11:147-151.

Hänninen OO, Alm S, Katsouyanni K, Kunzli N, Maroni M, Nieuwenhuijsen MJ, et al. 2004a. The EXPOLIS study: implications for exposure research and environmental policy in Europe. *J Expo Anal Environ Epidemiol* 14:440-456.

Hänninen OO, Lebret E, Ilacqua V, Katsouyanni K, Kunzli N, Sram RJ, et al. 2004b. Infiltration of ambient PM<sub>2.5</sub> and levels of indoor generated non-ETS PM<sub>2.5</sub> in residences of four European cities. *Atmospheric Environment* 38:6411-6423.

Hänninen OO, Palonen J, Tuomisto JT, Yli-Tuomi T, Seppanen O, Jantunen MJ. 2005. Reduction potential of urban PM2.5 mortality risk using modern ventilation systems in buildings. *Indoor Air* 15:246-256.

Harkema JR, Wagner JG. 2005. Epithelial and inflammatory responses in the airways of laboratory rats coexposed to ozone and biogenic substances: enhancement of toxicant-induced airway injury. *Exp Toxicol Pathol* 57 Suppl 1:129-141.

Instanes C, Hetland G, Berntsen S, Lovik M, Nafstad P. 2005. Allergens and endotoxin in settled dust from day-care centers and schools in Oslo, Norway. *Indoor Air* 15:356-362.

Institute of Medicine Committee on Damp Indoor Spaces and Health. 2004. *Damp Indoor Spaces and Health*. Washington, DC:National Academies Press.

Jantunen MJ, Hanninen O, Katsouyanni K, Knoppel H, Kuenzli N, Lebret E, et al. 1998. Air pollution exposure in European cities: The "EXPOLIS" study. *Journal of Exposure Analysis and Environmental Epidemiology* 8:495-518.

Jarvis BB. 2003. *Stachybotrys chartarum*: a fungus for our time. *Phytochemistry* 64:53-60.

Jong SC, David EE. 1976. Contribution to the knowledge of *Stachybotrys* and *Memnoniella* in culture. *Mycotaxon* 3:409-485.

Karol MH. 2002. Respiratory allergy: what are the uncertainties? *Toxicology* 181-182:305-10.:305-310.

Keswani J, Kashon ML, Chen BT. 2005. Evaluation of interference to conventional and real-time PCR for detection and quantification of fungi in dust. *J Environ Monit* 7:311-318.

Kilburn S, Lasserson TJ, McKean M. 2003. Pet allergen control measures for allergic asthma in children and adults. *Cochrane Database Syst Rev* CD002989.

Koistinen KJ, Edwards RD, Mathys P, Ruuskanen J, Kunzli N, Jantunen MJ. 2004. Sources of fine particulate matter in personal exposures and residential indoor, residential outdoor and workplace microenvironments in the Helsinki phase of the EXPOLIS study. *Scand J Work Environ Health* 30 Suppl 2:36-46.

Koschel D, Stark W, Karmann F, Sennekamp J, Muller-Wening D. 2005. Extrinsic allergic alveolitis caused by misting fountains. *Respir Med* 99:943-947.

Krieger JK, Takaro TK, Allen C, Song L, Weaver M, Chai S, et al. 2002. The Seattle-King County healthy homes project: implementation of a comprehensive approach to improving indoor environmental quality for low-income children with asthma. *Environ Health Perspect* 110 Suppl 2:311-322.

Kuhn DM, Ghannoum MA. 2003. Indoor mold, toxigenic fungi, and Stachybotrys chartarum: infectious disease perspective. *Clin Microbiol Rev* 16:144-172.

Larson T, Gould T, Simpson C, Liu LJ, Claiborn C, Lewtas J. 2004. Source apportionment of indoor, outdoor, and personal PM<sub>2.5</sub> in Seattle, Washington, using positive matrix factorization. *J Air Waste Manag Assoc* 54:1175-1187.

Laumbach RJ, Kipen HM. 2005. Bioaerosols and sick building syndrome: particles, inflammation, and allergy. *Curr Opin Allergy Clin Immunol* 5:135-139.

Li Y, Duan S, Yu IT, Wong TW. 2005a. Multi-zone modeling of probable SARS virus transmission by airflow between flats in Block E, Amoy Gardens. *Indoor Air* 15:96-111.

Li Y, Huang X, Yu IT, Wong TW, Qian H. 2005b. Role of air distribution in SARS transmission during the largest nosocomial outbreak in Hong Kong. *Indoor Air* 15:83-95.

Lioy PJ. 2006. Employing dynamical and chemical processes for contaminant mixtures outdoors to the indoor environment: The implications for total human exposure analysis and prevention. *J Expo Sci Environ Epidemiol.*

Magari SR, Schwartz J, Williams PL, Hauser R, Smith TJ, Christiani DC. 2002. The association between personal measurements of environmental exposure to particulates and heart rate variability. *Epidemiology* 13:305-310.

Mar TF, Koenig JQ, Jansen K, Sullivan J, Kaufman J, Trenga CA, et al. 2005. Fine particulate air pollution and cardiorespiratory effects in the elderly. *Epidemiology* 16:681-687.

Marklund A, Andersson B, Haglund P. 2003. Screening of organophosphorus compounds and their distribution in various indoor environments. *Chemosphere* 53:1137-1146.

McConnell R, Jones C, Milam J, Gonzalez P, Berhane K, Clement L, et al. 2003. Cockroach counts and house dust allergen concentrations after professional cockroach control and cleaning. *Ann Allergy Asthma Immunol* 91:546-552.

McDevitt JJ, Lees PS, Merz WG, Schwab KJ. 2004. Development of a method to detect and quantify *Aspergillus fumigatus* conidia by quantitative PCR for environmental air samples. *Mycopathologia* 158:325-335.

McKone TE, Knezovich JP. 1991. The transfer of trichloroethylene (TCE) from a shower to indoor air: experimental measurements and their implications. *J Air Waste Manage Assoc* 41:832-837.

Meklin T, Haugland RA, Reponen T, Varma M, Lummus Z, Bernstein D, et al. 2004. Quantitative PCR analysis of house dust can reveal abnormal mold conditions. *J Environ Monit* 6:615-620.

Meng QY, Turpin BJ, Korn L, Weisel CP, Morandi M, Colome S, et al. 2005. Influence of ambient (outdoor) sources on residential indoor and personal PM<sub>2.5</sub> concentrations: analyses of RIOPA data. *J Expo Anal Environ Epidemiol* 15:17-28.

Menzies D, Popa J, Hanley JA, Rand T, Milton DK. 2003. Effect of ultraviolet germicidal lights installed in office ventilation systems on workers' health and wellbeing: double-blind multiple crossover trial. *Lancet* 362:1785-1791.

Meyer HW, Jensen KA, Nielsen KF, Kildeso J, Norn S, Permin H, et al. 2005. Double blind placebo controlled exposure to molds: exposure system and clinical results. *Indoor Air* 15 Suppl 10:73-80.

Molhave L, Kjaergaard SK, Sigsgaard T, Lebowitz M. 2005. Interaction between ozone and airborne particulate matter in office air. *Indoor Air* 15:383-392.

Morgan WJ, Crain EF, Gruchalla RS, O'connor GT, Kattan M, Evans R, III, et al. 2004. Results of a home-based environmental intervention among urban children with asthma. *N Engl J Med* 351:1068-1080.

Morris RD. 2001. Airborne particulates and hospital admissions for cardiovascular disease: a quantitative review of the evidence. *Environ Health Perspect* 109 Suppl 4:495-500.:495-500.

Morrison GC, Nazaroff WW. 2002. Ozone interactions with carpet: secondary emissions of aldehydes. *Environ Sci Technol* 36:2185-2192.

Nazaroff WW. 2004. Indoor particle dynamics. *Indoor Air* 14 Suppl 7:175-83.:175-183.

Nazaroff WW, Singer BC. 2004. Inhalation of hazardous air pollutants from environmental tobacco smoke in US residences. *J Expo Anal Environ Epidemiol* 14 Suppl 1:S71-S77.

Nielsen KF, Huttunen K, Hyvarinen A, Andersen B, Jarvis BB, Hirvonen MR. 2002. Metabolite profiles of Stachybotrys isolates from water-damaged buildings and their induction of inflammatory mediators and cytotoxicity in macrophages. *Mycopathologia* 154:201-205.

Oie L, Hersoug LG, Madsen JO. 1997. Residential exposure to plasticizers and its possible role in the pathogenesis of asthma. *Environ Health Perspect* 105:972-978.

Ott W, Wallace L, Mage D. 2000. Predicting particulate (PM10) personal exposure distributions using a random component superposition statistical model. *J Air Waste Manag Assoc* 50:1390-1406.

Ott WR, Roberts JW. 1998. Everyday exposure to toxic pollutants. *Sci Am* 278:86-91.

Pandian MD, Behar JV, Ott WR, Wallace LA, Wilson AL, Colome SD, et al. 1998. Correcting errors in the nationwide data base of residential air exchange rates. *J Expo Anal Environ Epidemiol* 8:577-586.

Pauley SM. 2004. Lighting for the human circadian clock: recent research indicates that lighting has become a public health issue. *Med Hypotheses* 63:588-596.

Pope CA III, Verrier RL, Lovett EG, Larson AC, Raizenne ME, Kanner RE, et al. 1999. Heart rate variability associated with particulate air pollution. *Am Heart J* 138:890-899.

Pope C, Dockery D, Spengler J, Raizenne M. 1991. Respiratory health and PM 10 pollution: a daily times series analysis. *Am Rev Respir Dis* 144:668-674.

Reiss R, Ryan PB, Tibbetts SJ, Koutrakis P. 1995. Measurement of organic acids, aldehydes, and ketones in residential environments and their relation to ozone. *J Air Waste Manag Assoc* 45:811-822.

Rumchev K, Spickett J, Bulsara M, Phillips M, Stick S. 2004. Association of domestic exposure to volatile organic compounds with asthma in young children. *Thorax* 59:746-751.

Sallis JF, Glanz K. 2006. The role of built environments in physical activity, eating, and obesity in childhood. *Future Child* 16:89-108.

Salthammer T, Bednarek A, Fuhrmann F, Funaki R, Tanabe S-I. 2002. Formation of organic indoor air pollutants by UV-curing chemistry. *Journal of Photochemistry and Photobiology A: Chemistry* 152:1-9.

Samet JM, Spengler JD, Mitchell CS. 1998. Indoor air pollution. In: *Environmental and Occupational Medicine* (Rom WN, ed.). Philadelphia:Lippincott-Raven Publishers, 1523-1537.

Schmeichel D, Simpson JP, Beezhold D, Lewis DM. 2006. The development of species-specific immunodiagnostics for *Stachybotrys chartarum*: the role of cross-reactivity. *J Immunol Methods* 309:150-159.

Sebastian A, Szponar B, Larsson L. 2005, Characterization of the microbial community in indoor environments by chemical marker analysis: an update and critical evaluation. *Indoor Air* 15 Suppl 9:20-26.

Sexton K, Greaves IA, Church TR, Adgate JL, Ramachandran G, Tweedie RL, et al. 2000. A school-based strategy to assess children's environmental exposures and related health effects in economically disadvantaged urban neighborhoods. *J Expo Anal Environ Epidemiol* 10:682-694.

Sexton K, Adgate JL, Church TR, Ashley DL, Needham LL, Ramachandran G, et al. 2005. Children's exposure to volatile organic compounds as determined by longitudinal measurements in blood. *Environ Health Perspect* 113:342-349.

Sexton K, Adgate JL, Ramachandran G, Pratt GC, Mongin SJ, Stock TH, et al. 2004. Comparison of personal, indoor, and outdoor exposures to hazardous air pollutants in three urban communities. *Environ Sci Technol* 38:423-430.

Shoemaker RC, House DE. 2005. A time-series study of sick building syndrome: chronic, biotoxin-associated illness from exposure to water-damaged buildings. *Neurotoxicol Teratol* 27:29-46.

Spannhake EW, Reddy SP, Jacoby DB, Yu XY, Saatian B, Tian J. 2002. Synergism between rhinovirus infection and oxidant pollutant exposure enhances airway epithelial cell cytokine production. *Environ Health Perspect* 110:665-670.

Stevens RG. 2005. Circadian disruption and breast cancer: from melatonin to clock genes. *Epidemiology* 16:254-258.

Terr AI. 2004. Are indoor molds causing a new disease? *J Allergy Clin Immunol* 113:221-226.

Thatcher TL, Layton DW. 1995. Deposition, resuspension, and penetration of particles within a residence. *Atmospheric Environment* 29:1487-1497.

Thomas KW, Pellizzari ED, Clayton CA, Whitaker DA, Shores RC, Spengler J, et al. 1993. Particle Total Exposure Assessment Methodology (PTEAM) 1990 study: method performance and data quality for personal, indoor, and outdoor monitoring. *J Expo Anal Environ Epidemiol* 3:203-226.

Tobias KR, Ferriani VP, Chapman MD, Arruda LK. 2004. Exposure to indoor allergens in homes of patients with asthma and/or rhinitis in southeast Brazil: effect of mattress and pillow covers on mite allergen levels. *Int Arch Allergy Immunol* 133:365-370.

Venn AJ, Cooper M, Antoniak M, Laughlin C, Britton J, Lewis SA. 2003. Effects of volatile organic compounds, damp, and other environmental exposures in the home on wheezing illness in children. *Thorax* 58:955-960.

Vesper SJ, Varma M, Wymer LJ, Dearborn DG, Sobolewski J, Haugland RA. 2004. Quantitative polymerase chain reaction analysis of fungi in dust from homes of infants who developed idiopathic pulmonary hemorrhaging. *J Occup Environ Med* 46:596-601.

Viegi G, Simoni M, Scognamiglio A, Baldacci S, Pistelli F, Carrozzi L, et al. 2004. Indoor air pollution and airway disease. *Int J Tuberc Lung Dis* 8:1401-1415.

Vineis P, Husgafvel-Pursiainen K. 2005. Air pollution and cancer: biomarker studies in human populations. *Carcinogenesis* 26:1846-1855.

Wainman T, Weschler CJ, Lioy PJ, Zhang J. 2001. Effects of surface type and relative humidity on the production and concentration of nitrous acid in a model indoor environment. *Environ Sci Technol* 35:2201-2206.

Wallace L. 1996. Indoor Particles: A Review. *Journal of the Air & Waste Management Assoc* 46:98-126.

Wallace L, Nelson W, Ziegenfus R, Pellizzari E, Michael L, Whitmore R, et al. 1991. The Los Angeles TEAM Study: personal exposures, indoor-outdoor air concentrations, and breath concentrations of 25 volatile organic compounds. *J Expo Anal Environ Epidemiol* 1:157-192.

Weich S, Blanchard M, Prince M, Burton E, Erens B, Sproston K. 2002. Mental health and the built environment: cross-sectional survey of individual and contextual risk factors for depression. *Br J Psychiatry* 180:428-433.

Weisel CP, Zhang J, Turpin BJ, Morandi MT, Colome S, Stock TH, et al. 2005. Relationship of Indoor, Outdoor and Personal Air (RIOPA) study: study design, methods and quality assurance/control results. *J Expo Anal Environ Epidemiol* 15:123-137.

Weschler CJ. 2004. Chemical reactions among indoor pollutants: what we've learned in the new millennium. *Indoor Air* 14 Suppl 7:184-94.:184-194.

Weschler CJ, Brauer M, Koutrakis P. 1992. Indoor ozone and nitrogen dioxide: a potential pathway to the generation of nitrate radicals, dinitrogen pentaoxide, and nitric acid indoors. *Environ Sci Technol* 26:179-184.

Weschler CJ, Shields HC. 1996. Production of the hydroxyl radical in indoor air. *Environ Sci Technol* 30:3250-3258.

Weschler CJ, Shields HC, Naik DV. 1989. Indoor ozone exposures. *JAPCA* 39:1562-1568.

Weschler CJ, Wells JR, Poppendieck D, Hubbard H, Pearce TA. Indoor Chemistry and Health - A Workshop Summary. *Environ Health Perspect* Online 3 Nov 2005. 113-2005.

Xu X, Weisel CP. 2005. Human respiratory uptake of chloroform and haloketones during showering. *J Expo Anal Environ Epidemiol* 15:6-16.

Zhang J, Wilson WE, Liou PJ. 1994. Sources of organic acids in indoor air: a field study. *J Expo Anal Environ Epidemiol* 4:25-47.